Remarks

Applicants have amended the specification to correct clerical errors noted by the Examiner. Attached hereto is a marked-up version of the changes made to the specification by the current amendments, captioned "Version With Markings To Show Changes Made." The amendments are fully supported by the specification and claims as originally filed, and thus no new matter has been added.

Claims 23-80 will be pending upon entry of these amendments. Applicants respectfully request reconsideration of the objection and rejections in view of the following remarks.

I. Amendment of the Specification

Applicants have amended the specification to correct several clerical errors noted by the Examiner. In particular, Applicants have corrected sequence identifiers and figure references on pages 13-16 and 19-20.

The amendments to the specification are fully supported by the specification and figures as originally filed. Accordingly, no new matter has been added by way of amendment, and entry of the above amendments is respectfully solicited.

II. Rejoinder

The Examiner has indicated that even upon the indication of allowable subject matter, rejoinder of the claims of Group XXIX will not be permitted. (*See* Paper No. 10, pages 3-4). In particular, while the Examiner asserts that Groups XXIX and XXXIV are related as product and process of use, the Examiner maintains the allegation that Groups XXIX and XXXIV are distinct.

In response, Applicants point out that the process claims of Group XXXIV either depend from or otherwise include all of the limitations of the product claims of Group XXIX. Pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), if an elected product claim is found allowable, "withdrawn process claims which depend from or otherwise include all of the limitations of the allowable product claim will be rejoined." M.P.E.P. § 821.04. Thus, Applicants submit that even assuming *arguendo* that the claims of Groups XXIX and XXXIV are distinct, rejoinder is permitted by M.P.E.P. § 821.04. Accordingly, Applicants respectfully request that if any of the claims of Group XXIX are found allowable, then the process claims of Group XXXIV be rejoined and examined for patentability.

III. Objection to the Specification

The Examiner has objected to the to the specification because it contains clerical errors in the sequence identifiers and figure references on pages 13-16 and 19-20. (Paper No. 10, Page 4). In response, Applicants thank the Examiner for noting the obvious clerical errors. Applicants have corrected the clerical errors in the sequence identifiers and figure references on pages 13-16 and 19-20, and thus submit that the Examiner's objection has been fully addressed. Accordingly, it is respectfully requested that the Examiner's objection to the specification be reconsidered and withdrawn.

IV. Rejection of the Claims under 35 U.S.C. §§ 101 and 112, First Paragraph.

The Examiner has rejected claims 23-80 under 35 U.S.C. § 101 because the invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility. (*See* Paper No. 10, Pages 4-8). In particular, the Examiner alleges

that "the specification fails to assert any utility for the claimed polynucleotides or the encoded proteins." The Examiner also asserts that "credibility cannot be assessed." Further, the Examiner alleges that because the BM-HABP of the present invention has a higher degree of identity to Q9NRY3 (Tao et al.) and Q9UF98 (Blum et al.) than to Mus musculus TSG-6, "the protein of the present invention can not be identified as a member of 'TSG-6 (HABP)' family." The Examiner has further rejected claims 23-80 under 35 U.S.C. § 112, first paragraph, because one skilled in the art would allegedly not know how to use the claimed invention, based on the supposed lack of either a specific substantial asserted utility or a well- established utility.

Applicants respectfully disagree and traverse these rejections.

As a preliminary matter, Applicants note that the Examiner has acknowledged that the specification asserts more than one utility (*see* Paper No. 10, pages 5 & 7; Specification at pages 20 & 210-332). Applicants also point out that the Examiner has not challenged the credibility of the utilities asserted in the specification. Rather, the Examiner has questioned whether the disclosed utilities are specific and substantial (Paper No. 10, Page 5). Applicants respectfully assert that, as discussed in detail below, the specification discloses multiple specific, substantial, and credible utilities for the present invention.

"When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. § 101 is clearly shown." *Raytheon v. Roper,* 724 F.2d 951, 958, 220 U.S.P.Q. 592, 598 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 835 (1984); *see also* M.P.E.P. §§ 2107.01(II) – (III) (7th Ed. Rev. 1, Feb. 2000) at 2100-29; Utility Examination Guidelines, 66 Fed. Reg. 1092, 1098 (January 5, 2001). In order to find that an asserted utility is not specific or substantial, the burden is on the Examiner to make a *prima facie*

showing that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant would be specific or substantial. *See* Utility Examination Guidelines at 1098, col. 3. Such a *prima facie* showing must contain (1) an explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not both specific and substantial nor well-established; (2) support for factual findings relied upon in reaching this conclusion; and (3) an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. *See id.* Moreover, the burden is on the Examiner to establish why it is more likely than not that one of ordinary skill in the art would doubt *(i.e.,* "question") the truth of the statement of utility. *See* M.P.E.P. § 2107.01(II)(A); Utility Examination Guidelines at 1098-99. Thus, the Examiner must provide evidence sufficient to show that a statement of asserted utility would be considered "false" by a person of ordinary skill in the art. *See id.* The Examiner must also present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the applicants' assertion of utility. *See id.*; *see also In re Brana,* 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). For the reasons set forth below, the Examiner has not met the burden that is necessary to establish and maintain a rejection for lack of utility under 35 U.S.C. § 101.

As the Examiner recognized in the Office Action at page 5, the specification points out that the BM-HABP of the present invention is structurally analogous to the TSG-6 family of hyaluronan-binding proteins, and should have similar biological activities to members of that family based on the shared structure. (*See* Specification at page 20, lines 21-33 (as amended); Figure 8). Based on such asserted activities, and contrary to the Examiner's comments, the specification provides guidance to the skilled artisan to use the BM-HABP of the present invention for similar purposes as TSG-6, including but not

limited to: binding hyaluronan, and playing a vital role in arthritis, anti-inflammatory activity, and the vascular injury response. (*See* Specification at page 20, lines 28-33). Applicants assert that such characterization of the invention is sufficient to constitute a showing of utility, as the utility of the instant BM-HABP protein is clearly asserted in the specification.

Indeed, Applicants point out that the Utility Examination Guidelines require an evaluation of the utilities taught in the closest prior art (in the instant case, TSG-6). *See* Utility Examination Guidelines at 1098. However, the Examiner fails to credit the substantial homology present, and instead argues that if TSG-6 and BM-HABP had similar activities, the homology would be greater between them than between BM-HABP and the Q9NRY3 and Q9UF98 proteins of Tao et al. and Blum et al., respectively. Applicants respectfully disagree, and further point out that this argument addresses credibility, rather than whether the asserted utilities are specific and substantial. Nevertheless, Applicants note that Tao et al. also teach that their protein contains a hyaluronan-binding domain. (*See* Reference AD, submitted herewith). Thus, this reference cited by the Examiner further confirms the asserted function and utility of the BM-HABP of the present invention. The Examiner has not alleged that either Tao et al. or Blum et al. teach inconsistent uses for their respective proteins. Accordingly, the Examiner has not met the burden of making a *prima facie* showing that Applicants' asserted utility is not credible. Further, Applicants point out that the Examiner has failed to provide evidence sufficient to show that the above asserted utilities would be considered "false" by a person of ordinary skill in the art.

The Examiner has also failed to address all of the utilities disclosed by the specification, beyond a conclusory statement that "these activities are not demonstrated."

Applicants note that this is not the test for utility- rather, the Examiner must make a *prima facie* showing that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant would be specific or substantial. The test as to specificity is whether an asserted utility is specific to the subject matter claimed, in contrast to a utility that would be applicable to the broad class of the invention. Applicants respectfully assert that the disclosed utilities for BM-HABP discussed above are specific, in that, for example, not every protein binds hyaluronan, or plays a vital role in arthritis, anti-inflammatory activity, and the vascular injury response. Applicants further assert that the disclosed utilities for BM-HABP discussed above are substantial, as "the general rule [is] that the treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." (Revised Interim Utility Guidelines Training Materials, p. 6) In addition, although the Examiner states that the credibility of the asserted utilities has not been addressed in the Office Action, Applicants submit that these utilities are not only credible, but indeed true, especially in light of the well-known uses of TSG-6.

Applicants respectfully point out that their position coincides with that of the United States Patent and Trademark Office ("USPTO") as set forth in the recently published Revised Interim Utility Guidelines Training Materials. In particular, the USPTO's discussion of therapeutic proteins at pages 27-29 makes clear that the above disclosed utilities are specific and substantial. *See also* Example 10, "DNA Fragment encoding a Full Open Reading Frame (ORF)," at pages 53-55. Thus, in agreement with the USPTO's own commentary, and contrary to the Examiner's position, Applicants assert that the instant invention does indeed satisfy the utility requirement.

In regard to these asserted therapeutic activities, Applicants note that there is no need to prove that a correlation exists between a particular activity and an asserted

therapeutic use of a compound as a matter of statistical certainty or provide actual evidence of success in treating humans where such a utility is asserted. M.P.E.P. § 2107.02 (I) at 2100-33 to 2100-34. All that is required of Applicants is that there be a reasonable correlation between the biological activity and the asserted utility. *See Nelson v. Bowler*, 626 F.2d 853, 857 (C.C.P.A. 1980). Moreover, "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, *necessarily* includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana,* 51 F.3d 1560, 1568 (Fed. Cir. 1995) (emphasis added).

In view of the above, Applicants respectfully submit that the presently claimed invention possesses specific, substantial, and credible utilities which constitute patentable utilities under 35 U.S.C. § 101. Because Applicants' assertions of utility are sufficient to satisfy the requirements of 35 U.S.C. § 101, it is respectfully requested that the Examiner's rejection of claims 23-80 under 35 U.S.C. § 101 be reconsidered and withdrawn.

Further, the Federal Circuit and its predecessor determined that the utility requirement of 35 U.S.C. § 101 and the how to use requirement of 35 U.S.C. § 112, first paragraph, have the same basis, *i.e.*, the disclosure of a credible utility. *See In re Brana*, 51 F.3d 1560, 1564, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995); *see also* M.P.E.P. § 2107(IV); Utility Examination Guidelines at 1098. As discussed above, the specification teaches specific and well-established utilities of the claimed invention, thereby enabling the skilled artisan to use the claimed polypeptides. Since the specification contains a detailed description of how to use the claimed polypeptides, and the specification describes specific and immediate utilities for the claimed invention, the claimed invention

is enabled. Accordingly, it is respectfully requested that the Examiner's rejection of the claims under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

V. Rejection of Claims 31-32, 36-37, 41-44, 48-51, 55-68, and 72-77 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 31-32, 36-37, 41-44, 48-51, 55-68, and 72-77 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. (*See* Paper No. 10, Page 9). In particular, the Examiner alleges that the claims are indefinite "since it is unclear by absence in the claim whether or not the polypeptide fragments are active, or what that activity may be."

Applicants respectfully disagree and traverse this rejection.

Applicants point out that the instant claims are not limited to only biologically active fragments, or to fragments with only particular activities. Indeed, the specification specifically teaches the use of polypeptide fragments as immunogens to raise antibodies, which does not require biological activity. Thus, the claims do not need to state any activity in order to be definite, and the Examiner has provided no support for the instant rejection that suggesting otherwise. While the scope of the claims is broader than those limited to biologically active fragments, the breadth of a claim is not to be equated with indefiniteness. *See* M.P.E.P. § 2173.04; *In re Miller*, 441 F.2d 689, 169 U.S.P.Q. 597 (C.C.P.A. 1971). Applicants submit that the pending claims fully meet the requirements of 35 U.S.C. § 112, second paragraph, and respectfully request that the Examiner's rejection of the claims under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

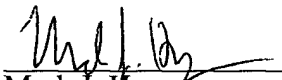
Conclusion

In view of the foregoing remarks, Applicants believe that this application is now in condition for allowance, and an early notice to that effect is urged. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above or in the Petition for an Extension of Time submitted concurrently herewith, such an extension is requested and the appropriate fee should also be charged to our Deposit Account.

Respectfully submitted,

Dated: August 3, 2001



Mark J. Hyman (Reg. No. 46,789)
Attorney for Applicants

Human Genome Sciences, Inc.
9410 Key West Avenue
Rockville, MD 20850
Telephone: (240) 314-1224

Enclosures

VIA HAND DELIVERY AUGUST 3, 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Hastings et al. Attorney Docket No.: PF487

Application Serial No.: 09/466,778 Art Unit: 1653

Filed: December 20, 1999 Examiner: Mitra, R.

Title: Novel Hyaluronan-Binding Proteins and Encoding Genes

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraphs from page 13, line 26 to page 14, line 23, have been rewritten as follows:

Figures 4A-B show the nucleotide sequence (SEQ ID NO:10) and deduced amino acid sequence (SEQ ID NO:11) of BM-HABP. The deduced complete amino acid sequence includes 353 amino acid residues and has a deduced molecular weight of about 36063.32 Da. The predicted domains of the BM-HABP polypeptide are: an HA binding motif domain (amino acid residues Q-121 to L-215 ~~in~~ of SEQ ID NO:11~~(SEQ ID NP:11)~~), double underlined.

Figures 5A-G show ~~shows~~ the regions of identity between the amino acid sequence of the full-length WF-HABP protein (SEQ ID NO:2) and the translation product of the human TSG-6 protein (SEQ ID NO:3; See Genbank Accession No. gi|339994), as determined by Megalign (DNA Star suite of programs) analysis. Identical amino acids between the two polypeptides are shaded, while the non-identical regions remain unshaded. By examining the regions of amino acids shaded and/or unshaded, the skilled artisan can readily identify conserved domains between the two polypeptides.

Figures 6A-B show ~~shows~~ the regions of identity between the amino acid sequence of the WF-HABP protein (SEQ ID NO:5) and the translation product of the human TSG-6 protein (SEQ ID NO:3; See Genbank Accession No. gi|339994), as determined by Megalign (DNA Star suite of programs) analysis. Identical amino acids between the two polypeptides are shaded, while the non-identical regions remain unshaded. By examining the regions of amino acids shaded and/or unshaded, the skilled artisan can readily identify conserved domains between the two polypeptides.

Figure ~~Figures~~ 7 shows the regions of identity between the amino acid sequence of the OE-HABP protein (SEQ ID NO:8) and the translation product of the Cartilage Link Protein from Gallus gallus (SEQ ID NO:9; See Genbank Accession No. gi|212260), as determined by Megalign (DNA Star suite of programs) analysis. Identical amino acids between the two polypeptides are shaded, while the non-identical regions remain unshaded. By examining the regions of amino acids shaded and/or unshaded, the skilled artisan can readily identify conserved domains between the two polypeptides.

Figure ~~Figures~~ 8 shows the regions of identity between the amino acid sequence of the BM-HABP protein (SEQ ID NO:11) and the translation product of the TSG-6 protein from Mus musculus (SEQ ID NO:12; See Genbank Accession No. 2062475), as determined by Megalign (DNA Star suite of programs) analysis. Identical amino acids between the two polypeptides are shaded, while the non-identical regions remain unshaded. By examining the regions of amino acids shaded and/or unshaded, the skilled artisan can readily identify conserved domains between the two polypeptides.

The paragraphs from page 15, line 17 to page 16, line 15, have been rewritten as follows:

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding a full-length WF-HABP polypeptide (Figures 1A-H (SEQ ID NO:2 ~~1~~)). The full-length WF-HABP protein shown in Figures 1A-H (SEQ ID NO:2) shares sequence homology with the human TSG-6 protein (Figures 5A-G (SEQ ID NO:3)).

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding a WF-HABP polypeptide (Figures 2A-B (SEQ ID NO:5 ~~6~~)), the amino acid sequence of which was determined by sequencing a cloned cDNA (Clone HWFBG79). The WF-HABP protein shown in Figures 2A-B (SEQ ID NO:5) shares sequence homology with human cartilage link protein (~~Figures~~ Figure 6 (SEQ ID NO:6)). The nucleotide sequence shown in Figures 2A-B (SEQ ID NO:4) was obtained by sequencing a cDNA clone (Clone HWFBG79). On December 1, 1998, the plasmid corresponding to this clone was deposited with the American Type Culture Collection, 10801 University Blvd, Manassas, Virginia, 20110-2209, and was assigned accession number 203503. The deposited cDNA is contained in the pBluescript plasmid (Stratagene, La Jolla, CA).

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding a OE-HABP polypeptide (Figures 3A-B (SEQ ID NO:8)), the amino acid sequence of which was determined by sequencing a cloned cDNA (Clone HOEDH76). The OE-HABP protein shown in Figures 3A-B (SEQ ID NO:8) shares sequence homology with the Gallus gallus cartilage link protein (~~Figures~~ Figure 7 (SEQ

ID NO:9)). The nucleotide sequence shown in Figures 3A-B (SEQ ID NO:7) was obtained by sequencing a cDNA clone (Clone HOEDH76). On December 1, 1998, the plasmid corresponding to this clone was deposited with the American Type Culture Collection, 10801 University Blvd, Manassas, Virginia, 20110-2209, and was assigned accession number 203501. The deposited cDNA is contained in the pBluescript plasmid (Stratagene, La Jolla, CA).

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding a BM-HABP polypeptide (Figures 4A-B (SEQ ID NO:11)), the amino acid sequence of which was determined by sequencing a cloned cDNA (Clone HBMVC21). The BM-HABP protein shown in Figures 4A-B (SEQ ID NO:11) shares sequence homology with the Mus musculus TSG-6 protein (Figures 8 (SEQ ID NO:12 ~~11~~)). The nucleotide sequence shown in Figures 4A-B (SEQ ID NO:10) was obtained by sequencing a cDNA clone (Clone HBMVC21). On December 1, 1998, the plasmid corresponding to this clone was deposited with the American Type Culture Collection, 10801 University Blvd, Manassas, Virginia, 20110-2209, and was assigned accession number 203502. The deposited cDNA is contained in the pBluescript plasmid (Stratagene, La Jolla, CA).

The paragraphs from page 19, line 16 to page 20, line 33, have been rewritten as follows:

The determined nucleotide sequence of the full-length WF-HABP cDNA of Figures 1A-H (SEQ ID NO:1) contains an open reading frame encoding a polytopic polypeptide of about 2100 amino acid residues, with a HA-binding domain, EGF-like

Type 1 domains, EGF-like Type 2 domains; laminin-type EGF domains; link protein domain; cytochrome P450 cysteine heme-iron ligand binding domains; a prokaryotic membrane lipoprotein lipid attachment site domains, and having a deduced molecular weight of about 231445.37 Da. The WF-HABP protein shown in Figures 1A-H (SEQ ID NO:2 ~~1~~) is predicted to contain domains which are about 48% identical to the human hyaluronan binding protein TSG-6 protein depicted in SEQ ID NO:6 (see Figures 5A-G ~~6A-B~~) using the computer program "MegAlign" (DNAstar suite of software programs). In addition to having homology, TSG-6 and the full-length WF-HABP are thought to share the same topological structure based upon their intrinsic hyaluronan binding activity. For example, like TSG-6, the full-length WF-HABP contains a hyaluronan binding domain. As discussed above, TSG-6 has been shown to be a hyaluronan binding protein and play a vital role in arthritis, antiinflammatory activity, and the vascular injury response.

The determined nucleotide sequence of the WF-HABP cDNA of Figures 2A-B (SEQ ID NO:4) contains an open reading frame encoding a polytopic polypeptide of about 457 amino acid residues, with a HA-binding domain, an EGF-like Type 2 domain, and a link protein domain, and having a deduced molecular weight of about 48448.90 Da. The WF-HABP protein shown in Figures 2A-B (SEQ ID NO:5 ~~2~~) is predicted to be about 48% identical to the human hyaluronan binding protein TSG-6 protein depicted in SEQ ID NO:6 (see Figures ~~6A-B~~) using the computer program "MegAlign" (DNAstar suite of software programs). In addition to having homology, TSG-6 and WF-HABP are thought to share the same topological structure based upon their intrinsic hyaluronan binding activity. For example, like TSG-6, WF-HABP contains a hyaluronan binding domain. As

discussed above, TSG-6 has been shown to be a hyaluronan binding protein and play a vital role in arthritis, antiinflammatory activity, and the vascular injury response.

The determined nucleotide sequence of the OE-HABP cDNA of Figures 3A-B (SEQ ID NO:7) contains an open reading frame encoding a polytopic polypeptide of about 289 amino acid residues, with a HA-binding domain, 6 transmembrane domains, 4 extracellular domains, and a pore loop, and having a deduced molecular weight of about 33174.55 Da. The OE-HABP protein shown in Figures 3A-B (SEQ ID NO:8) is predicted to be about 49% identical to the collagen link protein depicted in SEQ ID NO:9 (see Figures 7~~A-B~~) using the computer program "MegAlign" (DNAstar suite of software programs). In addition to having homology, collagen link protein and OE~~WF~~-HABP are thought to share the same topological structure based upon their intrinsic hyaluronan binding activity. For example, like collagen link protein, OE~~WF~~-HABP contains a hyaluronan binding domain. As discussed above, collagen link protein has been shown to be a hyaluronan binding protein and play a vital role in arthritis, antiinflammatory activity, and the vascular injury response.

The determined nucleotide sequence of the BM-HABP cDNA of Figures 4A-B (SEQ ID NO:10 ~~8~~) contains an open reading frame encoding a polytopic polypeptide of about 353 amino acid residues, with a HA-binding domain, 6 transmembrane domains, 4 extracellular domains, and a pore loop, and having a deduced molecular weight of about 36063.32 Da. The BM~~OE~~-HABP protein shown in Figures 4A-B (SEQ ID NO:11 ~~10~~) is predicted to be about 43% identical to the TSG-6 protein depicted in SEQ ID NO:12 ~~11~~ (see Figures 8~~A-B~~) using the computer program "MegAlign" (DNAstar suite of software programs). In addition to having homology, the TSG-6 protein and BM~~WF~~-HABP are

thought to share the same topological structure based upon their intrinsic hyaluronan binding activity. For example, like the TSG-6 protein, BM~~WF~~-HABP contains a hyaluronan binding domain. As discussed above, TSG-6 protein has been shown to be a hyaluronan binding protein and play a vital role in arthritis, antiinflammatory activity, and the vascular injury response.